PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Praveen SHARMA et al.** Conf. No.: **8084**

Appln. No.: **10/727,576** Group Art Unit: **1634**

Filed: **December 05, 2003** Examiner: **Juliet C. Switzer**

For: **METHOD OF PREPARING A STANDARD DIAGNOSTIC GENE TRANSCRIPT PATTERN**

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner of Patents
P.O. Box. 1450
Alexandria, Virginia 22313-1450

I, Dr James Mackay, a British citizen of 8 Hanover Street, London, W1S 1YE declare as follows:

1. The present Declaration is supplementary to the Declaration submitted March 27, 2009, executed by me and filed in relation to this application and included my background, credentials and a copy of my curriculum vitae.

2. I have been asked to provide my opinion on the Examiner's comments set out in the Official Letter dated 1 July 2009 (which I have reviewed) in which the sole objection remaining to the claims is one of lack of inventive step.

3. I am informed that the test for whether subject matter is considered inventive is whether a person of ordinary skill would have considered the claimed subject matter obvious over the prior art. I understand that the prior art should be interpreted as it would have been understood by the person of ordinary skill and that hindsight may not be used to interpret its teaching. I am also informed that even if the claimed subject matter is considered obvious to try it would only be considered obvious if there is a reasonable expectation of success.

4. The Examiner maintains that it is obvious to apply the method of Ralph *et al* to very early stage breast cancer (stage 0) diagnosis despite earlier submissions by the applicant and makes 3 particular points in this regard. Each of these points will be dealt with separately.

5. Firstly, the Examiner maintains that my previous comments (that the skilled person

would have understood Ralph *et al* to be based on the release of cancer cells, their debris, or celllular components into the blood system resulting in direct interaction between cancer cells and blood cells leading to altered expression), are in direct contrast to the teachings of Ralph *et al* as set out in column 5, lines 7-11 referring to very early stage disease detection "when there are few or no circulating diseased cells present in the peripheral blood".

6. My comments and the statements in Ralph *et al* are not at odds with one another. In the quoted passage Ralph *et al* refers to two alternatives, namely (i) when there are few circulating diseased cells and (ii) when there are no circulating diseased cells. The first alternative is entirely in line with my comments that a direct interaction would be considered necessary between cancer cells (or their components or debris) and blood cells. A few circulating cells are present and these can interact with blood cells. In the second alternative, although no circulating cells are present, this does not exclude the possibility that debris or cellular components of cancer cells are in the blood system and that these interact directly with the blood cells. This possibility was covered in my comments.

7 Not only are the comments made in my earlier Declaration not inconsistent with the statements in Ralph *et al*, but further, in view of the requirements for assessing inventive step, the relevant interpretation of Ralph *et al* is how the person of ordinary skill would interpret the document. It is clear that Ralph *et al* is principally concerned with the analysis of metastatic cancers and detection of markers for those cancers and the specification clearly mentions that this is the advance which was made by the invention described by Ralph *et al* (see column 5, lines 55 to 57; column 6, lines 62 to 67; column 7, lines 1 to 14; column 61, lines 12 to 18 and column 80, lines 32 to 35).

8. When considered in the context of the full document, whilst some references are made to organ confined cancers these are in reference to prostate cancers. Thus, Example 5 illustrates that one can diagnose organ confined prostate cancer using the methods of the specification.

9 As mentioned in my earlier Declaration, in paragraphs 4 and 5, the prostate cancers that were examined by Ralph *et al* were either metastatic or had metastatic potential and could have been expected to have released debris or cellular components into the peripheral blood system. Thus, in interpreting the data and comments provided in Ralph *et al* the skilled person would understand that the types of cancers which had been shown to be detectable had evidence of metastasis and thus any extrapolation to performing the methods of detection on other cancers would need to be performed on similar cancers, I.e. those cancers that are metastatic or have metastatic potential.

10. As such, on the basis of what was known about the cancers examined and the results obtained, to make sense of Ralph *et al*'s statement that the method could be performed when there were no (or few) circulating diseased cells, the person of ordinary skill would have expected that it was the debris or cellular components of cancer cells (which are a characteristic of early prostate cancers such as those which were examined by Ralph *et al*) which were responsible for the effects observed.

11. In my opinion, Ralph *et al* provides a method which identifies cancers which have begun to exhibit phenotypic changes which are evident on the cells, or debris or components from the cells. The phenotypic changes effectively provide markers of a metastatic phenotype. In my view these markers of a metastatic phenotype are detected in peripheral blood cells after those blood cells interact with that metastatic phenotype. The

metastatic phenotype would be evident in cancer cells or their debris or components which would begin to be released once metastatic potential had been reached. Thus, the Ralph *et al* method is limited to detecting cancers which have reached this metastatic potential or which are metastatic. In view of what was known about the cancers that Ralph *et al* examined, the person of ordinary skill would have understood that the Ralph *et al* method would only be capable of detecting such cancers

12. Whilst Ralph *et al* refers to early stages of disease, the person of ordinary skill would not interpret this as referring to very early stages of breast cancer in which metastatic potential has not been reached. In column 52, from line 1, Ralph *et al* indicates that in early stages of the disease the immune response may be localised. Ralph *et al* then refers to a metastasizing tumour. Therefore, Ralph *et al* is linking early stages of cancer to those which are metastasizing and not those which have not yet reached metastatic potential as would be the case in very early stage breast cancer stages which are the subject of the claims (see paragraphs 7 and 9 of my earlier Declaration).

13. There is no technical teaching from the Examples which have been reported in Ralph *et al* that would make the person of ordinary skill think that Ralph *et al* intends for the method to be extended to detection of cancers in which metastatic potential has not yet been reached. The comment that it may be feasible to look at very early stages of disease progression where there are few or no circulating cells needs to be viewed in this context, as discussed above in paragraph 12. Firstly, it is purely speculative whether very early stages of disease could be detected based on the disclosure of Ralph *et al.*, and secondly, even if a person of ordinary skill gave this comment credence, it would be considered in view of the disclosure of Ralph *et al* that this could only apply to cancers which have at least reached metastatic potential, e.g. organ defined prostate cancers.

14. Ralph *et al* makes no reference to the detection of very early stage breast cancers, with good reason. Organ defined breast cancers could not be expected to behave in the same way as organ defined prostate cancers as only the latter would reach metastatic potential in their very early stages. There would therefore be no expectation that the same principle (i.e. evidence of a metastatic phenotype) could be used to identify very early stage breast cancers which did not have a metastatic phenotype. Extension of the Ralph *et al* teaching to very early stage breast cancer is only possible with hindsight.

15. Further, even if the person of ordinary skill were to consider attempting to use the Ralph *et al* method for very early stage breast cancer detection, he would not have expected such cancers to be detectable by altered gene expression in peripheral blood samples. In very early stage breast cancer the cancer cells have not reached metastatic potential and have therefore neither released cells nor their components or debris into the blood system. In the absence of contact between blood cells and the cancer cells or their components or debris, no effects on gene expression in blood cells would be expected. Furthermore, since these cells have not reached metastatic potential, any debris that might be released into the blood system would not be indicative of a metastatic phenotype which forms the basis of the Ralph *et al* test. As a consequence there would be no expectation that such a detection method might be effective.

16 As mentioned in my earlier Declaration (paragraph 12), the present inventors have unexpectedly and surprisingly found that very early stage breast cancer can be detected in peripheral blood samples. In contrast, Ralph *et al* shows experiments in which only metastatic cancers or those with metastatic potential are detected. Thus, it was not

obvious that such detection methods could be applied to an entirely different group of cancers, i.e. those which had not yet reached metastatic potential. The application of the Ralph *et al* method to such cancers is not simply an extension of the method to other cancers which have similar properties and could therefore be expected to be effective, but would require extension to cancers which are quite distinct in location and properties and for which there was no evidence that any effects in peripheral blood cells might be observed. In the present application, detection of pre-metastatic stages of disease, i.e. before phenotypic changes typifying metastatis are evident and detectable, is possible. Since the Ralph *et al* method relies on detection of these changes it was entirely unexpected that detection of very early stage breast cancer in which no such changes had taken place was possible from analysis of peripheral blood cells.

17. The second point that the Examiner makes (last paragraph on page 3 of the Official Letter) is that the passages quoted in my previous Declaration to illustrate that direct contact is required between the sample to be analyzed and the diseased cells is in a section discussing immunodetection assays and not the identification of markers based on mRNA expression.

18. However, it is entirely artificial to segregate the teachings in relation to immunodetection assays and those relating to mRNA expression as the two effects are intimately linked. It is self-evident that if transcript levels are modified so too will be antigen levels as the former is a trigger for the latter. Thus comments made in relation to the requirements to achieve alterations in antigen expression must necessarily apply to the requirements to achieve alteration in mRNA expression as the alteration in mRNA expression is causal on changes in antigen expression. Furthermore, the column 52 passage is clearly not concerned with antigen detection since this refers to the effect on gene expression. Thus the comments in Ralph *et al* referring to direct contact cannot be dismissed since they are the stated basis of both the transcript variation and also any variations in the proteins that are expressed.

19 The third point raised by the Examiner (first paragraph of page 4 of the Official Letter) is that it was known at the time of the invention that white blood cells spent time in the interstitial fluid and lymphatic system and not just the circulatory system and so could have come into contact with tumour cells even if no blood vessels invaded the tumour. The Examiner links this to the teaching that detection is feasible when there are few or no circulating cancer cells. As mentioned above, the presence of few or no circulating cancer cells for detection of very early stage disease, such as organ confined prostate cancer is entirely feasible based on the metastatic potential of such cancers.

20 Ralph *et al* makes no mention that blood cells that are sampled in peripheral blood have been altered in terms of their gene expression by contact with tumour cells at the tumour site. Ralph *et al* contemplates that blood cells may contact tumour cells locally, but in those cases, suggests that a local sample is taken, see column 52, lines 1-4 which refers to the response being limited to lymph nodes surrounding a metastasising tumour or other localized form of a disease state in early states. This is also reflected in the samples which are contemplated (column 47, lines 17-26) which are not limited to peripheral blood samples.

21. More importantly, however, mere contact of a blood cell with a tumour cell is not enough. According to the Ralph *et al* method, as discussed above, the person of ordinary skill would have understood that the tumour cells would need to be ones with metastatic

potential or which were metastatic. Very early stage breast cancer cells are neither. Very early stage breast cancers are pre-metastatic. Clinical evidence supports this. 100% of DCIS may be resolved surgically as DCIS is entirely pre-metastatic. In contrast, only 40-60% of prostate cancers may be cured in this way which is evidence of the metastatic changes which have occurred in those cancers.

22. In summary, looking at the technical content of Ralph *et al* and the teachings in that document, it would be clear that Ralph *et al* have identified that cancers which are metastatic or which have metastatic potential may be detected in peripheral blood at early stages of that metastatic process, e.g. organ confined prostate cancer. The person of ordinary skill in the art would appreciate that this could be applied to similar instances to those which were tested, i.e., to other cancers which had reached metastatic potential or metastasis. However, there is no teaching either of a technical nature or within the description of Ralph *et al.* that would have allowed a person of ordinary skill to make the jump to the detection of cancers which had not yet reached metastatic potential by analysis of peripheral blood. Such cancers are in an entirely different category as they have not yet released cells, their components or debris into the peripheral blood and do not have a detectable metastatic phenotype. It would, therefore, have been understood by a person of ordinary skill in the art, that there were limits on the method disclosed by Ralph *et al* and the cancers to which it could be considered applicable. Based on the content of Ralph *et al* it is my view that the person of ordinary skill would not have expected that the methods disclosed in that document could be applied to very early stage breast cancer, a stage in which cancer cells are entirely confined to ducts of the breast and in which metastatic potential has not yet been reached and hence there is no metastatic phenotype. To apply the teaching of Ralph *et al* to such cancers requires knowledge gleaned from the present invention, which equates to hindsight.

23. The present invention provides surprisingly effective detection and identification of very early stage breast cancer by analysis of gene expression levels in peripheral blood cells, a method not rendered obvious by Ralph *et al.* Success in detecting early stage breast cancer would not have been expected based on the teaching of Ralph *et al.*

24. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Codes, and that such wilful false statements may jeopardize the validity of the application and any patent issuing thereon.

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Dr James Mackay Date